REMARKS

I. Introduction

In accordance with the foregoing, claims 1 and 26 have been amended. Claims 8, 12-19, and 21-22 have been cancelled. Claims 1-7, 10-11, and 23-26 are pending and under consideration.

The amendments to claims 1 and 26 are supported by the Specification of the present invention at page 14, lines 17 and 21-26, the examples, and Figure 1.

II. Claim rejections under 35 USC § 112, second paragraph

The Office Action asserts that claims 1-8, 10-19, and 21-25 are indefinite under 35 USC § 112. The Office Action argues that the terms "tetrose" and "pentose" are broad and inclusive of reducing sugars.

Because claim 1 has been amended to restrict the non-reducing sugar to a fructosyl group, the rejection above should be withdrawn with respect to claims 1-7, 10-11, and 23-25. Because claims 8, 12-19, and 21-22 have been canceled, their rejection has been overcome.

III. Claim rejections under 35 USC § 102(b)

The Office Action rejects claims 1-3, 5, 7, 10-14, 16, 18, and 21-22 under 35 U.S.C. § 102(b) as being anticipated by Kobayashi et al. (Int. J. Biol. Macromol. 1995, 17(6), 373-79). The Office Action asserts that Kobayashi et al. discloses the ß-glucan derivative of the present invention.

Regarding amended claim 1, Kobayashi et al. describes derivatives wherein the non-reducing sugar is a hexose having a terminal OMe group at the C-1 position (page 375, scheme 4). However, the hexose of Kobayashi et al. is glucose, while the non-reducing sugar of the ß-glucan derivative of amended claim 1 is fructose. Accordingly, the ß-glucan derivative of the present invention is different from the derivative of Kobayashi et al. Therefore, claims 1-3, 5, 7, 10, and 11 are novel over Kobayashi et al.

Furthermore, as to rejected claims 8, 12-19, and 21-22, these claims have been canceled.

IV. Claim rejections under 35 USC § 103

The Office Action rejects claims 4, 6, 8, 15, 17, 19 and 23-26 as being obvious over Kobayashi et al. (Int. J. Biol. Macromol. 1995, 17(6), 373-79) in view of Kokie et al. (ET 047-0331). The rejection of claims 8, 15, 17, and 19 has been rendered moot by the cancellation of these claims. The following arguments are directed to claims 4, 6, 15, and 23-26.

i) Regarding Kobayashi et al.

As discussed in Section III, the β-glucan derivative of amended claim 1 is different from the derivative of Kobayashi et al. Kobayashi et al. discloses a hexose having a terminal OMe group at the C-1. The Examiner interprets this as the non-reducing sugar. The β-glucan derivative of amended claim 1 uses a fructose is bonded to a reducing end.

The Office Action also asserts that Kobayashi et al. teaches the transfer of a non-reducing sugar to an oligosaccharide having a ß-glucan residue via the action of an enzyme such as cellulase. See Office Action at page 5.

However, the reaction of Kobayashi et al. is significantly different from the present invention. The Background Art section of the Specification describes the conventional methods which are used to inactivate the reducing end of a microcrystalline cellulose and cellulose powder. See Specification at page 3, lines 3-13. The reaction of Kobayashi et al. corresponds to the method where the reducing end is chemically modified by an enzyme. Id. at lines 12-13. In this method, when a sugar chain is added by transglucosylation mediated by a transferase or a hydrolase, it is most often the case that such transglucosylation proceeds from the non-reducing end of the sugar chain. Id. at lines 20-23. The Kobayashi et al. process requires the chemical modification (i.e. fluorination) of a glycosyl donor (see β-lactosyl fluoride in scheme 4) and the chemical modification at the C-1 position of a glycosyl acceptor (see methyl cellotrioside in scheme 4). Transglucosylation in Kobayashi et al. occurs at the non-reducing end of the sugar chain. Kobayashi et al. at scheme 4, page 375.

On the other hand, the present invention can obtain non-reducing ß-glucan without either of the Kobayashi et al. chemical modifications. According to the present invention, the non-reducing sugar may be transglucosylated to the reducing end of the ß-glucan residue without introducing protection groups. The product is advantageous in that it is produced faster with greater yields than could otherwise be accomplished.

Regarding claim 26, the Office Action further asserts that it would have been obvious to one of ordinary skill in the art to modify the Kobayashi et al. process so that transglucosylation occurs at the C-1 carbon bonded to the OMe group, instead of the sugar unit having a free hydroxyl group. Office Action at page 6. The Office Action argues that one having ordinary skill in the art would have recognized, "that if the sugar unit does not have an OME group at the C-1 (anomeric position) the same transglucosylation can happen there too." Id.

However, this is incorrect. As mentioned above, the method of Kobayashi et al. not only requires chemical modification to the acceptor molecule (i.e. addition of the OME group), but also the fluorination of the donor molecule. If these chemical modifications were eliminated, it would change the principal of operation of the Kobayashi et al. process because the reaction would proceed according to a different mechanism. See MPEP 2143.02 and MPEP 2145 III. at last paragraph.

The Office Action also argues that, "one of skill in the art would expect the [Kokie et al. process] to work for other oligosaccharides and would want to make polysaccharide and oligosaccharide's and their compositions." See Office Action at page 7-8, carryover paragraph. To support this proposition, the Office Action asserts that Kobayashi et al. at page 373, left column, second paragraph, teaches that such compounds have potential as polymeric drugs and biomaterials. Office Action at page 7-8, carryover paragraph.

However, Kobayashi et al. neither describes nor suggests that a useful product may be obtained from a fructose bound to a β-glucan having three or more glucose residues. Kobayashi et al. also does not teach or suggest that a useful product may be obtained when a fructose is bound to the reducing end of a microcrystalline cellulose and a cellulose powder, for example. More importantly, Kobayashi et al. discloses nothing about whether such a β-glucan derivative may be combined with an active ingredient having an amino group in a preparation without appreciable reaction between the active ingredient and the β-glucan derivative, and while maintaining the inherent moldability and disintegrability of the β-glucan derivatives. See Specification at paragraph [0005].

ii) Regarding Kokie et al.

The Office Action asserts that Kokie et al. discloses a process for preparing a fructose-containing oligosaccharide. The Office Action asserts that the Kokie et al. process comprises reacting an enzyme (β-fructofuranosidase) on a saccharide in the presence of aldose or ketose.

The Office Action further asserts Kokie et al., at page 2, lines 1-9, teaches that oligosaccharides and useful glycosides have physiological activity. Therefore, the Office Action argues, one would have been motivated to make the claimed compounds. Office Action at page 7-8, carryover paragraph.

However, Kokie et al. neither describes nor suggests that a useful product may be obtained from a fructose bound to a β-glucan having three or more glucose residues. Kokie et al. also does not teach or suggest that a useful product may be obtained when a fructose is bound to the reducing end of a microcrystalline cellulose and a cellulose powder. More importantly, Kokie et al. discloses nothing about whether such β-glucan derivatives may be combined with an active ingredient having an amino group without reacting with the active ingredient and while maintaining inherent moldability and disintegrability. See Specification at paragraph [0005].

iii) No motivation to combine the references, or expectation of success thereof

The Office Action argues that one having ordinary skill in the art would have been motivated to combine Kobayashi et al. with Kokie et al. to arrive at the claimed compounds.

As discussed above, the transglucosylation of Kobayashi et al. proceeds from a non-reducing end of a β-glucan residue, and chemical modification to both the donor and the receptor molecules is required for the reaction to work.

On the other hand, the reaction of Kokie et al. involves bonding the C-2 position of fructose to the C-1 position of glucose using β-fructofuranosidase. Kokie et al. page 7, lines 7-8, page 6, lines 34-38, page 8, lines 5-9 and 47-52.

Therefore, one of ordinary skill in the art would not have been motivated to combine the compounds of Kobayashi et al. with the compounds of Kokie et al. There is a distinct difference between the reaction mechanism of Kobayashi et al. and that of Kokie et al.

Nor would one of ordinary skill in the art have had a reasonable expectation that the "minor adjustment" suggested in the Office Action, would be successful. On page 6, the Office Action asserts,

> It can be seen that in Kobayashi's process glycosylation occurs at the sugar unit that has a free hydroxyl group (acceptor). So, one of ordinary skill in the art will recognize that if the sugar unit does not have an OME group at the C-1 (anomeric position) the same transglucosylation can happen there too. A **minor adjustment** in the structure of the beta glucan is needed to carry out the process instantly claimed and such a modification will be recognized by one

> of ordinary skill in the art and is also well within the skill level of the artisan. Id. (emphasis added).

However, Kobayashi et al. teaches that "because of the difficulties in realizing complete regio- and stereo-control of the glycosylated process between each monosaccharide unit, synthesis of [carbohydrate polymers such as cellulose is] extremely difficult." Kobayashi et al. at page 373 second paragraph. In describing scheme 4, cited by the Office Action, Kobayashi et al. teaches at page 375, right column, second full paragraph, "the reaction proceeds in a completely regio- and stereo-selective manner, giving rise to coupling products with β-1,4-glycosidic bonds exclusively." Further, Kobayashi et al. teaches that "the selective formation of cellulose I (parallel glucan chains) and cellulose II (anti-parallel glucan chains) is, to our best knowledge, the first successful example of controlling the relative direction of polymer chains at the polymerization stage." Kobayashi et al. at page 378 right column.

From these passages, it is clear that success of the minor adjustment suggested by the Office Action would have been anything but predictable. According to Kobayashi et al., the disclosed synthesis was pioneering work in an area of chemistry that had been resistant to progress. The difficulty experienced by practitioners in the art was that a synthesis could not be designed to link the monosaccharide units according to a specific stereochemistry (i.e. structure). The reactions of scheme 4 were able to achieve, presumably for the very first time, a very specific result according to a very specific reaction.

Further, one would actually have to make two adjustments to the reactants of Kobayashi et al. As discussed above, Kobayashi et al. modifies both the donor and acceptor molecules. Therefore, the results are much more difficult to predict than the single modification proposed by the Office Action.

iv) The claimed invention presents unexpected results over the cited references

Even if Kobayashi et al. and Kokie et al. could be combined and the Examiner established a *prima facie* case of obviousness, the present invention possesses improved or unexpected properties over the references.

To begin with, Kobayashi et al. and Kokie et al. disclose nothing of the special properties of the product. Kokie et al. only describes that the synthesis of oligosaccharides and useful glycosides known to have physiological activity were subject to intense study. Kokie et al. at page 2, lines 4-9. Kobayashi et al. only describes that homosaccharides and saccharides with a disaccharide repeating unit in the main chain have attracted attention from scientists due to their

potential as polymeric drugs and biomaterials. Kobayashi et al. at page 373, left column, second paragraph.

Neither reference discloses anything regarding the usefulness of a β-glucan derivative having three or more glucose residues and a fructose bound to the reducing end of the β-glucan. More importantly, neither reference discloses anything about whether such β-glucan derivatives may be combined in a preparation with an active ingredient having an amino group without a reaction between the active ingredient and the β-glucan derivative. Kobayashi et al. and Koki et al. do not suggest that nonreactivity between the β-glucan derivative and the active ingredient could be achieved by inactivating the amino-carbonyl reaction which would normally occur between the reducing end of a β-glucan derivative and a terminal amino group of the active ingredient. Finally, neither reference teaches that this nonreactivity could be achieved without sacrificing the inherent moldability and disintegrability of the β-glucan derivative. See Specification at paragraph [0005] and page 2, line 20 to page 3, line 1.

On the other hand, the Examples and Comparative Examples of the Specification demonstrate that the β-glucan derivatives of the present application possess such excellent and unexpected properties. In examples 1-4, a transglucosylated product of the present invention was mixed with L-arginine (an amino acid having several amine groups including a terminal amino group) and subjected to a storage stability test.[1] For each mixture, the decrease ratio in degree of whiteness was between 1-3%, and the white color appearance was maintained.

In contrast, the mixtures of the Comparative Examples were unsatisfactory. In Comparative Example 1, an equivalent mixture of Ceolus PH-101 (a β-glucan having 220 glucose residues, but no fructosyl group protection of the reducing end) with L-arginine was subjected to the storage stability test. As a result, the mixture turned yellow and the degree of whiteness decreased by 10%. In Comparative Example 2, a mixture of transglucosylated cellobiose (only two β-glucan residues) and L-arginine were similarly tested. Comparative Example 2 had poor moldability and easily disintegrated. Specification at page 31, line 13 to page 32, line 4. The hardness and the disintegration time of the Comparative Example 2 molded cylindrical products were 80N and 300 seconds, respectively. Specification at page 32, lines 2-4.

From the results of the Examples and Comparative Examples, it is clear that the present inventors have, for the first time, produced a cellulose powder or β-glucan derivative of three or

[1] The storage stability test, described on page 13, lines 4-26 of the Specification, is useful for determining whether a compound chemically interacts with an active ingredient over time.

more glucose residues having a reducing end that will not participate in an amino-carbonyl reaction with the terminal amino group of an active ingredient, and which will maintain moldability without disintegrating.

From the foregoing, it is clear that the compounds of the present invention have excellent and advantageous properties. These properties would not have been expected from the cited references, alone or in combination, by one having ordinary skill in the art at the time the invention was made. Therefore, claims 4, 6, and 23-26 are non-obvious over Kobayashi et al. and Kokie et al. Applicants respectfully request that the rejection of claims 4, 6, and 23-26 be withdrawn.

CONCLUSION

There being no further outstanding objections or rejections, it is submitted that the application is in condition for allowance. An early action to that effect is courteously solicited.

Finally, if there are any formal matters remaining after this response, the Examiner is requested to telephone the undersigned to attend to these matters.

If there are any additional fees associated with filing of this Amendment, please charge the same to our Deposit Account No. 19-3935.

Respectfully submitted,

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